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Title

Prophylactic antibiotic regimens in tumour surgery (PARITY): a pilot multicentre randomised controlled trial.

Permalink

<https://escholarship.org/uc/item/41q7v3rq>

Journal

Bone & joint research, 4(9)

ISSN

2046-3758

Author

PARITY Investigators

Publication Date

2015-09-01

DOI

10.1302/2046-3758.49.2000482

Peer reviewed

BJR



■ ONCOLOGY

Prophylactic antibiotic regimens in tumour surgery (PARITY)

A PILOT MULTICENTRE RANDOMISED CONTROLLED TRIAL

The PARITY Investigators

From McMaster University, Hamilton, Ontario, Canada

Objective

Clinical studies of patients with bone sarcomas have been challenged by insufficient numbers at individual centres to draw valid conclusions. Our objective was to assess the feasibility of conducting a definitive multi-centre randomised controlled trial (RCT) to determine whether a five-day regimen of post-operative antibiotics, in comparison to a 24-hour regimen, decreases surgical site infections in patients undergoing endoprosthetic reconstruction for lower extremity primary bone tumours.

Methods

We performed a pilot international multi-centre RCT. We used central randomisation to conceal treatment allocation and sham antibiotics to blind participants, surgeons, and data collectors. We determined feasibility by measuring patient enrolment, completeness of follow-up, and protocol deviations for the antibiotic regimens.

Results

We screened 96 patients and enrolled 60 participants (44 men and 16 women) across 21 sites from four countries over 24 months (mean 2.13 participants per site per year, standard deviation 2.14). One participant was lost to follow-up and one withdrew consent. Complete data were obtained for 98% of eligible patients at two weeks, 83% at six months, and 73% at one year (the remainder with partial data or pending queries). In total, 18 participants missed at least one dose of antibiotics or placebo post-operatively, but 93% of all post-operative doses were administered per protocol.

Conclusions

It is feasible to conduct a definitive multi-centre RCT of post-operative antibiotic regimens in patients with bone sarcomas, but further expansion of our collaborative network will be critical. We have demonstrated an ability to coordinate in multiple countries, enrol participants, maintain protocol adherence, and minimise losses to follow-up.

Cite this article: *Bone Joint Res*;4:154–162

Keywords: Orthopaedic oncology; bone sarcoma; randomised controlled trials; antibiotics; pilot study

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doi:10.1302/2046-3758.49.
2000482 \$2.00

Bone Joint Res
2015;4:154–162.
Received 25 June 2015; Accepted
after revision 23 September 2015

Article focus

- Clinical studies of patients with bone sarcomas have been challenged by insufficient numbers at individual centres to draw valid conclusions.
- The objective of this study was to assess the feasibility of conducting a definitive multi-centre randomised controlled trial (RCT) to determine whether a five-day regimen of post-operative antibiotics in comparison to a 24-hour regimen decreases surgical site infections (SSIs) in patients undergoing endoprosthetic reconstruction for lower extremity primary bone tumours.

- The authors determined feasibility by measuring patient enrolment, completeness of follow-up, and protocol deviations for the antibiotic regimens.

Key messages

- It is feasible to conduct a definitive multi-centre RCT of post-operative antibiotic regimens in patients with bone sarcomas.
- The authors demonstrated an ability to coordinate in multiple countries, enrol participants, maintain protocol adherence, and minimise losses to follow-up.

- In total, 15% of the participants in this study experienced a SSI.

Strengths and limitations

- There is no precedent for conducting large-scale surgical trials in this field.
- Pilot studies are often essential before embarking on large clinical trials because they can demonstrate feasibility, help manage resources, and build a collaborative network.
- This pilot RCT represents the first ever multi-centre RCT in sarcoma surgery.
- Further expansion of the PARITY network will be critical moving forward

Introduction

The current standard of care for most skeletally mature patients with lower extremity bone sarcomas is limb salvage surgery, which typically involves tumour resection, followed by functional limb reconstruction with modular metallic and polyethylene endoprosthetic implants.¹⁻³ Owing to the complexity and length of these procedures, as well as the immunocompromised nature of patients treated with chemotherapy, the risk for post-operative surgical site infection (SSI) is high.^{4,5}

Post-operative endoprosthetic SSIs often require staged revision surgery and long-term intravenous (IV) antibiotic therapy. Even following this management, repeat infection and ultimate amputation are common.⁴ Patient function and quality of life can be dramatically impacted, as can healthcare costs owing to extended hospital stays and multiple re-operations.^{6,7} The most effective post-operative regimen of prophylactic antibiotics to prevent SSIs following endoprosthetic reconstruction for lower extremity bone tumours is unknown, and current practice among orthopaedic oncological surgeons is highly varied.⁸

Bone sarcomas are rare forms of cancer, and clinical studies of patients with bone sarcomas have been challenged by insufficient numbers at individual centres to draw valid conclusions.⁹ Sarcomas represent < 1% of all malignancies, and bone sarcomas affect just four to five patients per million persons each year.¹⁰ High-quality collaborative research that can guide clinical practice for patients with bone sarcomas has lagged behind other orthopaedic surgery subspecialties, and there have been no multi-centre randomised controlled trials (RCTs) previously conducted in the field of orthopaedic oncological surgery.

Our earlier work has demonstrated high rates of SSI following the treatment of long bone tumours by surgical excision and endoprosthetic reconstruction;¹¹ highly varied opinion and practice among orthopaedic oncologists regarding prophylactic antibiotic regimens;⁸ an absence of applicable RCT evidence;^{9,11} and extensive support from investigators for a definitive RCT to evaluate a five-

day regimen of post-operative antibiotics in comparison with a 24-hour regimen of post-operative antibiotics.^{8,12}

In this pilot study, our primary objective was to assess the feasibility of conducting a definitive multi-centre RCT to determine whether a five-day regimen of post-operative antibiotics, in comparison with a 24-hour regimen of post-operative antibiotics, decreases the rate of SSI within one year in patients undergoing endoprosthetic reconstruction for lower extremity primary bone tumours. Our secondary objective was to determine the overall rate of SSI within one year of follow-up in patients undergoing wide resection and endoprosthetic reconstruction for lower extremity primary bone tumours.

Patients and Methods

Study design and setting. We performed a pilot international multi-centre blinded parallel two-arm RCT. Each participating site obtained local institutional research ethics board approval and all patients provided informed consent. This trial was registered at ClinicalTrials.gov (NCT01479283) and is reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement and recommendations for pilot studies.^{13,14} We have previously reported our study protocol in further detail.¹²

Participants/study subjects. We included patients who were 12 years of age or older and had lower extremity primary bone malignancies, benign aggressive tumours, or soft-tissue sarcomas which had invaded bone and required surgical excision and endoprosthetic reconstruction.

We excluded patients if they had any of the following:

- Known methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *enterococcus* skin colonisation;
- Documented anaphylaxis or angioedema to cefazolin or penicillin;
- Prior surgery within the surgical field (excluding a biopsy);
- Prior local infection within the surgical field;
- Known immunologically-deficient conditions of disease such as HIV (not including recent chemotherapy);
- Known renal insufficiency with estimated creatinine clearance (eGFR) of < 54 mL/min;
- Reconstruction planned to include allograft (bone transplant);
- Likely problems, according to the judgment of the investigators, with maintaining follow-up;
- Unable to provide consent.

Randomisation. An unblinded pharmacist at each site randomised participants during surgery to either five days or 24 hours of post-operative prophylactic cefazolin. We used a central internet-based computer-generated randomisation system that concealed allocation. Our randomisation protocol included randomly permuted blocks of two or four and was stratified by location of tumour (femur vs tibia) and study centre.

The participants, surgeons, healthcare providers other than the pharmacists, data collectors, outcome assessors, data analysts, and those interpreting the results, were blinded to treatment allocation. Sites that used pre-mixed antibiotic bags kept them shrouded as there was a visible difference between pre-mixed bags and saline.

Interventions. Our protocol instructed that all participants would receive 2 g of IV cefazolin pre-operatively within 60 minutes of their procedures, and 2 g of IV cefazolin every three to four hours intra-operatively. Post-operatively, participants received either five days or 24 hours of cefazolin according to their randomised treatment assignments:

- Participants in the five-day arm received 2 g of IV cefazolin post-operatively every eight hours for five days.
- Participants in the 24-hour arm received 2 g of IV cefazolin post-operatively every eight hours for 24 hours, followed by sham doses of IV saline (placebo) for an additional four days.
- Paediatric participants received doses of cefazolin or sham that were based on 100 mg/kg/day doses, but were otherwise identical to the adult regimens.

Surgical excision and endoprosthetic reconstruction were performed according to the standard practice of the participating surgeons, which typically involved a wide extensile exposure, isolation and protection of major neurovascular structures, and resection of the segment of bone affected by tumour with a 2 cm to 3 cm bone margin. Decisions about implant selection, surgical techniques, soft-tissue reconstruction, or post-operative care other than antibiotic therapy, were left at the discretion of the treating surgeons, but were recorded in our Case Report Forms.

Follow-up

We followed participants at two and six weeks; three, six, and nine months; and one year post-operatively. Trained research personnel collected all data prospectively according to standardised procedures, and the Case Report Forms were transmitted to a central Methods Center using a secure electronic data capture system (iDataFax, Clinical DataFax Systems Inc., Hamilton, Ontario, Canada). Other communication with individual sites was conducted via email, written letters, telephone conversations, and meetings in person.

Outcome measures. In order to evaluate feasibility, we measured patient screening and enrolment, completeness of follow-up at each time point, and protocol deviations for the pre-, intra-, and post-operative antibiotic regimens.

The treating surgeons, study coordinators, and/or their delegates at each site identified potentially eligible patients at presentation and classified them as eligible and included, eligible but missed, or excluded. Completeness of follow-up was calculated relative to the number of patients eligible for follow-up at each time point.

We recorded protocol deviations whenever a pre-, intra-, or post-operative dose was missed, given incorrectly, or supplemented with additional non-study antibiotics. When patients were discharged before five days after surgery, we discontinued their study treatments early, recorded a protocol deviation for the missed doses, and no further antibiotics were given.

We pre-specified our criteria for success of the pilot as enrolment of our pilot sample within two years, 70% or greater protocol adherence, and 95% or greater completeness to follow-up.

To evaluate SSI rates, the participating surgeons diagnosed superficial, deep, or organ/space SSI according to the definition of the Centers for Disease Control and Prevention (CDC), which specifies that at least one of the following criteria be met within one year after surgery:^{12,15}

- Purulent drainage from the incision;
- Organisms isolated from an aseptically-obtained culture of fluid or tissue from the incision;
- Incision deliberately opened by surgeon and culture positive;
- Incision deliberately opened by surgeon or designee and not cultured, but the patient has at least one of: pain, tenderness, localised swelling, redness, or heat;
- Diagnosis of a superficial/deep/organ space incisional SSI by surgeon.

Monitoring. Before the start of patient screening and enrolment at each site, the Methods Center collected and reviewed the following documents:

- Site Principal Investigator's current Curriculum Vitae;
- Physician's Clinical Trial Application;
- Confirmation of ethics approval from the local institutional ethics committee;
- Approved informed consent form(s);
- Site delegation and signature log;
- Qualified Investigator Undertaking Form, if applicable;
- Research Ethics Board Attestation Form, if applicable;

Thereafter, the Methods Center ensured that the Site Principal Investigator, Research Coordinator, and Pharmacy Designee had received appropriate study-specific training, which may have included review of the training presentation during a teleconference call, independent review of the training presentation by the site personnel, or attendance at an Investigator/Coordinator meeting.

During the participant follow-up and clinical data collection phase of the study, the Methods Center remotely conducted the following ongoing monitoring activities:

- Review quality control reports from the iDataFax system to identify sites with unacceptable amounts of missing data or unresolved queries;
- Review enrolment reports to identify sites which have not been submitting screening data;
- Review the tracking database to identify any inconsistencies between the randomisation system and the submitted Case Report Forms with respect to treatment allocation;

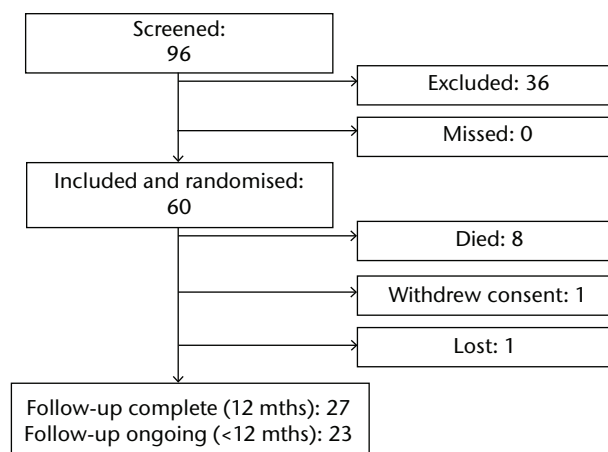


Fig. 1

Flow chart of participants in the trial.

- Review site-specific reports on study completion and loss to follow-up;
- Conduct periodic reviews of the site regulatory binders for missing and incomplete documentation;
- Review pharmacy logs.

After all subject follow-ups were completed at a clinical site, the Methods Center conducted the following remote closeout monitoring activities:

- Ensure that any missing data have been submitted (if available) and that all remaining data queries have been resolved;
- Ensure that all required adjudication materials have been submitted;
- Review the site regulatory file for completion and request any outstanding documentation;
- Review pharmacy logs;
- Request that the site close out the study with the local ethics board and submit a copy of the confirmation from the ethics committee to Chief Executive Officer for the site regulatory file

An independent Data Safety and Monitoring Board (DSMB) comprised of three orthopaedic surgeons and a statistician monitored participant safety. The DSMB reviewed adverse events and serious adverse events data on a quarterly basis, met via teleconference at least once a year, and was governed by a DSMB charter with terms of reference and functions.

Statistical analysis and study size. Baseline characteristics, feasibility data, and SSI rates are summarised as means with standard deviation (SD) or medians with interquartile range (IQR) for continuous variables and counts (%) for categorical variables. All analyses were conducted centrally at the Methods Center. Data analysis did not occur at any of the participating sites.

We enrolled a convenience sample of 60 participants to evaluate feasibility and we considered our pilot study completed when the last enrolled participant had

achieved at least three months of follow-up. We estimated that 60 patients would represent approximately 5% to 10% of the definitive RCT sample size (600 to 1200 patients), based on a pairwise comparison with an alpha of 0.05, a beta of 0.20 (80% power), a relative risk reduction of 50%,⁸ and a range of plausible SSI rates.^{12,16} We planned *a priori* to transition directly from our pilot RCT to a definitive RCT if feasibility was established, with the pilot event rate used to inform the definitive sample size estimation.

Results

Recruitment. We screened 96 patients across 21 clinical sites in Canada, the United States, Australia, and Argentina between November 2012 and October 2014. Of these, 60 were eligible and included, none were eligible but missed, and 36 were excluded (Fig. 1). The number of participants enrolled at each site in this period ranged from zero (six sites) to 18 (one site), but the initiation of screening and enrolment was staggered across the participating sites because of variability in the time required to obtain ethics approval and negotiate institutional contracts (Table I). In total, 20 of the sites reported having a dedicated research nurse or research coordinator available to assist with the conduct of the trial, and 14 reported prior institutional research experience for clinical trials. Notwithstanding our inclusion and exclusion criteria, the mean estimated number of endoprosthetic reconstructions performed at each site per month was 1.8 (SD 1.7).

By October 2014, 11 sites had been open for recruitment for 12 months or more, six sites had been open for six to 12 months, and four sites had been open for less than six months. The mean rate of enrolment in the trial after 'enrolment-ready' status was achieved was a mean of 2.13 (SD 2.4) participants per year across all sites.

Table I. Participating sites

Hospital	Institution	Country	Date opened to enrolment	Estimated number of EPRs per month	Research nurse	Research assistant	Prior clinical trials experience
Mount Sinai Hospital	University of Toronto	Canada	November 2012	2.0	Yes	Yes	Yes
The Ottawa Hospital	University of Ottawa	Canada	November 2012	1.0	Yes	No	Yes
Vancouver General Hospital	University of British Columbia	Canada	December 2012	1.5	Yes	No	Yes
Hôpital Maisonneuve - Rosemont	University of Montreal	Canada	December 2012	2.0	Yes	Yes	No
Juravinski Hospital and Cancer Centre	McMaster University	Canada	January 2013	0.3	Yes	Yes	No
McGill University Health Centre	McGill University	Canada	January 2013	2.0	Yes	No	Yes
Huntsman Cancer Institute	University of Utah	United States	February 2013	5.0	Yes	Yes	Yes
Vanderbilt Medical Center	Vanderbilt University School of Medicine	United States	March 2013	4.5	Yes	No	No
Hospital Universitario Austral	Universidad Austral	Argentina	May 2013	1.5	Yes	Yes	No
Beth Israel Deaconess Medical Center	Harvard Medical School	United States	July 2013	0.8	Yes	No	Yes
Saint-François d'Assise et L'Hotel-Dieu de Quebec	Laval University	Canada	November 2013	0.6	Yes	Yes	Yes
Memorial Sloan - Kettering Cancer Center	Cornell University	United States	December 2013	6.0	Yes	Yes	Yes
Royal Adelaide Hospital	University of Adelaide	Australia	December 2013	1.2	No	No	Yes
Holden Comprehensive Cancer Center	University of Iowa	United States	October 2013	0.6	Yes	No	No
Boston Children's Hospital	Harvard Medical School	United States	February 2014	0.8	Yes	No	Yes
University of Connecticut Health Center	University of Connecticut	United States	February 2014	0.3	Yes	No	No
Wexner Medical Center	The Ohio State University	United States	April 2014	4.5	Yes	No	Yes
University of Minnesota Medical Center	University of Minnesota	United States	June 2014	1.0	Yes	No	Yes
Emory Orthopaedics and Spine Center	Emory University	United States	July 2014	1.7	Yes	Yes	No
Stanford University Hospital and Clinics	Stanford University	United States	August 2014	0.6	No	Yes	Yes
The Rothman Institute	Thomas Jefferson University	United States	September 2014	0.8	Yes	Yes	Yes

EPR, endoprosthetic reconstruction

Baseline characteristics. The baseline characteristics of the 60 participants are presented in Table II. There were 44 men and 16 women, and their mean age was 41.2 years (SD 23). The most common tumour location was femur (88%), and the most common tumour type was osteosarcoma (48%). In total, 47% underwent pre-operative chemotherapy, and 17% had metastatic disease at baseline.

Feasibility. As of 24 March 2015, 27 patients completed 12 months of follow-up, 23 patients had completed < 12 months but were still active in the trial, eight patients had died, one had withdrawn consent the day after surgery, and one had been lost to follow-up (Fig. 1). Of the patients that were eligible for each follow-up visit, complete data were collected for 98% at two weeks, 100% at six weeks, 86% at three months, 83% at six months, 90% at nine months, and 73% at one year (Table III). A further 17% of the patients eligible for follow-up at one year had partially complete data, and 10% had pending queries.

In total, 58 participants were randomised on the day of surgery, one was randomised on the first day after surgery, and one was randomised on the day before surgery. Protocol deviations occurred for the pre-, intra-, or post-operative antibiotic regimens of 37 participants (61%) (Table IV). Pre-operatively, three patients did not receive 2 g of IV cefazolin within 60 minutes of their procedures and three patients received other antibiotics in addition to cefazolin according to local institutional protocols, and in accordance with per-site stratification. Intra-operatively, seven patients received doses of IV cefazolin other than 2 g every three to four hours owing to dosage adjustments for patient weight, and one patient received other antibiotics in addition to cefazolin.

Post-operatively, 18 participants missed at least one dose of cefazolin or placebo: 14 doses were missed among 11 participants because of pharmacy or nursing errors; 23 doses were missed among five participants because they were discharged before five days after surgery; 15 doses were missed in one participant who was

Table II. Baseline characteristics (n (%)) unless otherwise specified).

Characteristic	Patients (n = 60)
Mean age (yrs) (SD)	41.2 (23)
Women	16 (27)
Mean weight (kg) (SD)	73.2 (18)
Location of tumour*	
Femur	53 (88)
Tibia	7 (12)
Other (acetabulum/ilium)	1 (2)
Type of tumour†	
Osteosarcoma	28 (48)
Giant cell tumour of bone	3 (5)
Non-osteogenic sarcoma of bone	5 (8)
Chondrosarcoma	12 (20)
Ewing's sarcoma	4 (7)
Other‡	7 (12)
Metastases at baseline	
Yes	10 (17)
No	50 (83)
Diabetic	4 (7)
Tobacco use	
No	45 (75)
Yes	6 (10)
Yes, quit	9 (15)
Alcohol use	
Yes	24 (40)
No	36 (60)
Recreational IV drug use	
Yes	0 (0)
No	60 (100)
Undergone other treatment modalities	
No	32 (53)
Yes	28 (47)
Pre-operative chemotherapy	28
Pre-operative radiation	0
Other	0

* One patient has both femur and tibia

† n = 59 (one patient died before surgery, and no tumour characteristics form received)

‡ Epithelioid hemangioma with atypical features, fibrous dysplasia, high grade leiomyosarcoma, leiomyosarcoma, lymphoma of bone, pleomorphic sarcoma, synovial chondromatosis

Table III. Summary of completeness of follow-up

	Eligible for follow-up*	Completed (row %)	Partially complete (row %)	Missed (row %)	Outstanding (row %)
2 weeks	57	56 (98)	1 (2)	0 (0)	0 (0)
6 weeks	57	57 (100)	0 (0)	0 (0)	0 (0)
3 months	57	49 (86)	7 (12)	0 (0)	1 (2)
6 months	47	39 (83)	7 (15)	1 (2)	0 (0)
9 months	40	36 (90)	2 (5)	2 (5)	0 (0)
12 months	30	22 (73)	5 (17)	0 (0)	3 (10)

* Number of participants that reached each time point and not died, been lost, or withdrawn

started on alternative antibiotics after an intra-operative complication that led to a staged procedure; and 15 doses were missed in the participant who was randomised before surgery because they died before going to the operating room. The proportion of post-operative doses of cefazolin or placebo that were administered per protocol was 833 out of 900 (93%). Four patients received other antibiotics in addition to cefazolin post-operatively within the first five days after surgery.

SSI

Nine participants (15%) experienced SSI: six were organ/space, two were deep, and one was superficial. All eight of the organ/space or deep SSIs were treated with a re-operation (13%), and the superficial SSI was treated without a re-operation. Three of the SSIs were recorded at the six-week follow-up visits, two SSIs each were recorded at the three- and six-months visits, and one SSI each was recorded at the two-week and one-year visits.

Table IV. Protocol deviations for pre-, intra-, and post-operative antibiotic regimens. Data are presented as absolute numbers (%)

Protocol deviation	Patients (n = 60)
Pre-operative antibiotics	
Missed dose	3 (5)
Incorrect dose	0 (0)
Received additional antibiotics	3 (5)
Intra-operative antibiotics	
Missed at least one dose	0 (0)
Incorrect dose	7 (12)
Received additional antibiotics	1 (2)
Post-operative antibiotics	
Missed at least one dose	18 (30)
Incorrect dose	1 (2)
Received additional antibiotics	4 (7)

Discussion

The rarity of bone sarcomas dictates that multi-centre international collaboration is necessary in order to power surgical trials adequately in orthopaedic oncology. There is no precedent for conducting large-scale surgical trials in this field, however, and this pilot RCT represents the first ever multi-centre RCT in sarcoma surgery.⁹ Pilot studies are often essential before embarking on large clinical trials because they can demonstrate feasibility, help manage resources, and build a collaborative network.¹⁴ In this study, we established the feasibility of conducting a definitive large multi-centre RCT by enrolling of our pilot sample within two years, and demonstrating high protocol adherence with minimal losses to follow-up.

Limitations. We required 24 months to enrol 60 patients across 21 sites from four countries. After accounting for variability in the timing of start-up at the clinical sites, our mean enrolment rate was 2.13 participants per site per year. Our screening data suggest that every eligible patient was enrolled (no patients were missed), but it is also possible that some eligible patients were not screened at all. For example, the most common type of tumour in our study was osteosarcoma, and the United States Cancer Statistics Working Group reported nearly equivalent incidence rates of osteosarcoma in men and women (5.0 per million vs 5.1 per million, respectively),¹⁰ however, we enrolled more men than women in our study, which raises the possibility of selection bias at the participating sites. Data from the Surveillance, Epidemiology, and End Results database, however, suggested higher incidence of osteosarcoma in men (5.4 per million vs 4.0 per million, respectively).¹⁷

Nevertheless, the most likely factor leading to the imbalance of male *versus* female participants is our small sample size and the subsequent likelihood of chance alone leading to the uneven gender distribution.¹⁸ This factor further highlights the critical importance of conducting large randomised trials as they ensure a balance of both known and unknown prognostic variables through the randomisation process.

Our recruitment data suggest that the most critical factor for the success of our definitive trial will be further expansion of our collaborative network. At the time of manuscript submission, the PARITY network consisted of 66 sites: 28 sites are open to enrolment, 30 sites are in various stages of ethics review or contracts negotiation, and eight further sites have expressed interest. With the addition of these sites to the collaborative network, we anticipate that the pace of enrolment will continue to accelerate.

The primary outcome for our definitive trial will be the rate of SSIs in each arm within one year after surgery, an endpoint that relies heavily on subjective clinical judgments.¹⁹ Although the surgeons in our pilot were blinded, it is possible our pilot event rate could be biased towards under reporting, given their involvement in the cases or that there could have been variability in the way that the CDC criteria were applied. In order to minimise bias and variability in the definitive PARITY trial, the definitive trial will implement a blinded Central Adjudication Committee in order to evaluate all potential SSIs according to pre-defined criteria.²⁰

Feasibility. Sarcoma patients require intense oncological follow-up to monitor for disease relapse, and we anticipated only minimal losses to follow-up in our pilot sample, but we also implemented several procedures in order to minimise losses.²¹ Although only 73% of the patients eligible for one-year follow-up had complete data available, we consider that our data support feasibility because there were only three patients with outstanding queries at 12 months, and a further 17% of eligible patients had at least partial data available. Given that some of the pilot patients are still within their one-year follow-up period, we expect to resolve most or all of these outstanding queries and missing data. Only one patient was lost to follow-up, although one additional patient withdrew consent on the first day after surgery. With respect to data quality in relation to participating site characteristics, we believe that in the pilot phase of this trial there was a learning curve for all sites, and reporting of data quality by site at this stage would be premature.

More than half of the participants experienced minor protocol deviations related to their peri-operative antibiotics, but the importance of these deviations to the validity and feasibility of a definitive trial is doubtful. Ten participants did not receive the correct regimens of pre- and intra-operative antibiotics, but it is implausible that these errors could introduce systematic bias, because allocation was concealed. Three participants received additional antibiotics pre-operatively according to local institutional protocols, but stratification should randomly distribute these deviations evenly between groups. Trials with protocol deviations can be considered within a 'mechanistic-practical' framework of design and interpretation, whereby mechanistic trials address the impact of interventions administered under ideal testing circumstances, and practical trials address the impact of interventions administered in 'real world' clinical practice.²² Given that most of the protocol deviations in our study reflected typical clinical practice, and that 93% of all post-operative doses were administered per protocol, these protocol deviations are unlikely to compromise the practical applicability of our results.

Furthermore, many previous trials in orthopaedic surgery have not adequately reported protocol deviations.²³ However, we reported according to the CONSORT statement and recommendations for pilot studies in order to improve the design and conduct of a subsequent large definitive trial.¹⁴ The doses missed because of pharmacy, nursing, or randomisation errors will be used as feedback to guide our future standard operating procedures.

We coordinated an expert panel of six orthopaedic oncology surgeons and three infectious disease specialists in preparation for this study.^{8,12,24} Based on our survey data, expert opinion, and standard of care, we determined that the most appropriate antibiotic for this study was cefazolin. Our choice of five days as the long duration reflects consensus that an even longer duration would increase the risk for resistant organisms without providing further antimicrobial effectiveness.²⁵ We standardised the pre- and intra-operative antibiotic regimens in order to limit differential co-interventions.

Rates of SSI. In total, 15% of the participants in this study experienced a SSI. This rate exceeds the weighted mean of 9.5% identified in our systematic review (95% confidence interval (CI) 8.1 to 11.0), but this finding is not surprising, because most of the studies in our systematic review were retrospective case series at risk for selection bias or under reporting, owing to outcomes assessment bias. Prior studies have also used widely varying diagnostic criteria, and only two reported use of the CDC criteria.¹¹

The minimum follow-up in this pilot was just three months, but others have reported a median interval from implantation to infection of 8.5 months.²⁶ Therefore, it is possible that we could have detected an absolute risk of infection higher than 15% if all patients were followed up to one year. To the extent that this is true, a sample size

calculation based on our pilot data might conservatively over power our definitive PARITY RCT, which would reduce the likelihood of reporting a spuriously negative result. Our pilot data support the idea that minimal or no adjustments to the definitive sample size calculation are required for losses to follow-up.

In conclusion, it is feasible to conduct a definitive multicentre RCT of post-operative antibiotic regimens in patients with bone sarcomas, but further expansion of our collaborative network will be critical for study completion. We have demonstrated an ability to coordinate in multiple countries, enrol participants, maintain protocol adherence, and minimise losses to follow-up. The overall goal of PARITY is to provide high-quality evidence that can be used in the development of clinical guidelines. This pilot study has established a successful network and will support the rigorous design, organisation, and execution of a definitive RCT.

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Funding statement:

- This work was supported by grants from Physicians' Services Incorporated, Orthopaedic Research and Education Fund/Musculoskeletal Tumor Society, and Canadian Cancer Society Research Institute.
- This study was coordinated by the Center for Evidence-Based Orthopaedics at McMaster University

ICMJE Conflict of Interest:

- None declared

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Acknowledgements:

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